CELL-SPECIFIC IONIC MODELS OF CARDIAC PACEMAKER ACTIVITY

S. Dokos[1], S. L. Cloherty[1], N. H. Lovell[1], A. Zaza[2]
[1]Graduate School of Biomedical Engineering, University of New South Wales, Sydney, Australia
[2] Department of Biotechnology and Bioscience, University of Milan, Italy

Abstract-**We have developed a generic ionic model of single-cell rabbit sinoatrial node (SAN) electrical activity, employing Markov-state kinetics for membrane ionic currents. By suitable choice of parameters, the model is able to accurately reproduce a wide range of action potential waveforms recorded from individual SAN cells in the laboratory. Advantages of this approach include the ability to quantitatively investigate the contribution of ion currents underlying pacemaker and action potential activity from any given SAN myocyte recording.**
***Keywords* - Sinoatrial node, action potential, mathematical model.**

I. INTRODUCTION

Mammalian hearts generate self-sustaining rhythmic activity from trigger impulses arising from a region of pacemaker cells located in the wall of the right atrium known as the sinoatrial node (SAN). Biophysically-detailed mathematical models of single cell SAN electrical activity have been extensively published [1, 2], all based on Hodgkin-Huxley-type formalism to simulate underlying ionic membrane currents. Although yielding generic action potential waveforms crudely similar to those recorded in the laboratory, none of the models were able to accurately reproduce action potential waveforms from any specific SAN cell. This limits the usefulness of such models to quantitatively assess the contribution of underlying membrane currents to pacemaker activity, as well as the effects of various pharmacological agents, in any given SAN myocyte.

There is a need therefore, for a cell-specific approach in modelling SAN pacemaker activity, which can accurately simulate action potential waveforms recorded in the laboratory. In this study, we describe a new single cell SAN model employing Markov-state kinetic descriptions of ion currents, capable of highly-accurate reproduction of action potential waveforms recorded from specific SAN myocytes.

II. MODEL DESCRIPTION

The SAN cell model developed in this study consists of 12 membrane currents, acting in parallel across a capacitive cell membrane, with transmembrane E potential given by

$$\frac{dE}{dt} = \frac{-i_{tot}}{C} \tag{1}$$

with total membrane current i_{tot} given by the algebraic sum of its 12 constituents:

$$i_{tot} = i_f + i_{K,r} + i_{K,s} + i_{b,Na} + i_{Na} + i_p + \ldots \\ i_{NaCa} + i_{to} + i_{Ca,L} + i_{Ca,T} + i_{b,K} + i_{b,Cl} \tag{2}.$$

A brief description of the currents in (2) is summarized in table 1. All time-dependent currents were described using 3 or 4 Markov-state kinetic schemes, as outlined in table 1. These kinetic schemes represent conformational changes in membrane-spanning proteins controlling the flow of ions across the cell membrane. With reference to table 1, stable states of the underlying channel are denoted by C (closed), A (activated or open), and I_1, I_2 (inactivated). Forward and reverse rate constants between states is a function of membrane potential according to

$$k = k_\infty + \frac{k_0 - k_\infty}{1 + \exp\left[\frac{(E - E_{50})}{E_{slope}}\right]} \tag{3}.$$

This equation defines a sigmoidal-type profile for rate k as a function of membrane potential defined by 4 parameters: k_∞, k_0 (the values of k at $E=\pm\infty$), E_{50} (the E value at 50% of k's range) and E_{slope} (related to the slope at $E = E_{50}$). Each rate in the kinetic schemes of table 1 is given by (3), each having its own set of 4 parameters.

The general form for all time-dependent currents was given by

$$i = gA(E - E_{rev}) \tag{4}$$

with g denoting the membrane conductance, E_{rev} the reversal potential, and A the proportion of membrane channels in the open state. Default conductances and rate parameters in (3) and (4) were chosen to fit published voltage-clamp data for each ion current.

Using the default values of all model parameters as a starting point, a total set of 175 parameters were adjusted to fit a variety of pre-recorded single cell action potential SAN waveforms using a custom non-linear optimization routine developed for this purpose. All rate parameters were constrained to lie within ±30% of default values, and all ion current peaks were constrained to lie within physiological limits. This ensured that the contribution of all membrane currents to pacemaker activity was in accordance with commonly reported experimental values. A final constraint was that all ionic species K^+, Na^+, Ca^{2+} and Cl^- should exhibit no cycle-cycle drift.

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Abstract

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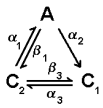
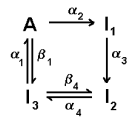
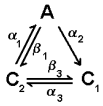
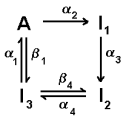
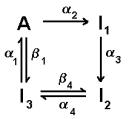
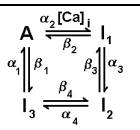
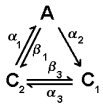
TABLE I
SUMMARY OF MEMBRANE CURRENTS IN SAN CELL MODEL

Symbol	Name	Kinetic Scheme
i_f	Hyperpolarization-activated current	
$i_{K,r}$	Rapid delayed-rectifying K^+ current	
$i_{K,s}$	Slow delayed-rectifying K^+ current	
$i_{b,Na}$	Background Na^+ current	(time-independent)
i_{Na}	TTX sensitive Na^+ current	
i_p	Na^+-K^+ pump current	(time-independent)
i_{NaCa}	Na^+-Ca^{2+} exchange current	(time-independent)
i_{to}	Transient outward current (incorporating 4-AP-sensitive sustained outward current i_{sus})	
$i_{Ca,L}$	L-type Ca^{2+} current	
$i_{Ca,T}$	Transient Ca^{2+} current	
$i_{b,K}$	Background K^+ current	(time-independent)
$i_{b,Cl}$	Background Cl^- current	(time-independent)

III. RESULTS

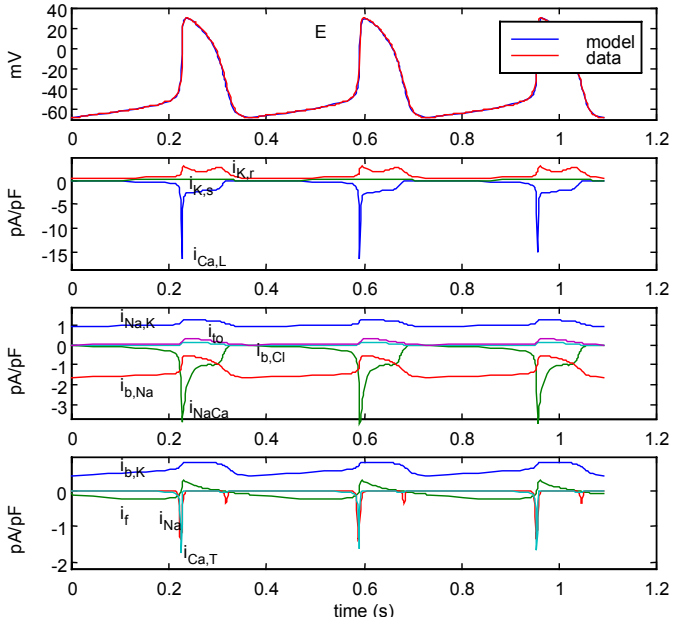


Fig. 1. Computational fit obtained to isolated single cell sinoatrial node recording. Top trace illustrates the near-exact overlap in action potential between the real cell and an ionic model. Lower traces reveal underlying model membrane currents. All initial variables, parameters and peak currents of the model were constrained to lie within physiological limits. Membrane currents were also constrained to yield zero mean ionic fluxes per cycle for steady-state periodic activity.

Figure 1 illustrates an example of one model fit to action potential waveform data recorded from an enzymatically-isolated SAN cell using the Nystatin patch technique. RMS error between the model waveform and the smoothed experimental recording was approximately 1 mV. The results of figure 1 reveal a marked improvement over previous models in matching action potential data recorded from real SAN cells. In addition, underlying current waveforms and amplitudes shown in this figure are well in agreement with generally accepted experimental findings.

IV. CONCLUSION

Ionic mechanisms underlying pacemaker activity in SAN cells can be investigated using the computational models of cellular electrical activity developed in this study. A major improvement over existing models is that model parameters have been adjusted to accurately reproduce action potential waveforms recorded from specific cells. This study represents the first stage in highly accurate modelling of ionic activity in any individual pacemaker cell.

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